Applicants are thankful to the Examiner for withdrawing the previous rejections under 35 U.S.C. §112, first paragraph, and the previous art rejections relying on inhibitory BB-1-specific B7-specific antibodies which inhibit the binding of B7.1 antigen to CTLA-4. In addition, Applicants respectfully thank the Examiner for acknowledging the Amendment filed October 14, 1997.

However, Applicants respectfully point out that a Petition to Correct Inventorship was filed January 8, 1998, which was not acknowledged in the Office Action dated January 16, 1998. Applicants realize that the paper may not have been matched to the file before the Examiner completed the Office Action. In view of the importance of this Petition, Applicants respectfully request verification in the next Office communication that this paper was received. Alternatively, verification may be made in a telephone call to the undersigned.

Although the previous art rejections have been withdrawn, the Office Action has set forth new rejections of claims 29-32 and 37 under 35 U.S.C. §102(b) as allegedly being anticipated by Razi-Wolf et al., Vallé et al. or Van Gool et al. Specifically, the Office Action asserts that "no more of a reference is required

than that it sets forth the substance of the invention." Applicants respectfully traverse.

The "substance of the present invention" is not taught by any of the cited references. All of the current claims are directed to a monoclonal antibody which specifically binds human B7.1 antigen (CD80), which inhibits the binding of human B7.1 antigen to CD28, but which does not inhibit the binding of B7.1 antigen to CTLA-4, and compositions containing the same.

The first cited reference, Razi-Wolf et al., makes absolutely no mention of CTLA-4. However, absent evidence to the contrary, the reasonable expectation would be that this antibody will inhibit the B7/CTLA-4 interaction given the known high level of homology between CD28 and CTLA-4.

Furthermore, the antibody disclosed by Razi-Wolf et al. differs from the claimed antibodies in that it is specific for murine B7-1, not human B7.1 as specifically recited in the claims. Thus, Razi-Wolf does not anticipate the claimed invention under 35 U.S.C. 102(b); it is axiomatic that anticipation of a claim under § 102 can be found only if the prior art reference discloses every element of the claim. In re King, 231 USPQ 136, 138 (Fed. Cir. 1986).

The second reference, Vallé et al., is said to allegedly anticipate the instant claims due to the disclosure of the B7-specific antibody 104. Again, Applicants respectfully traverse. Although Vallé et al. teaches a human monoclonal antibody, Vallé et al., likewise, makes absolutely no mention of CTLA-4. Thus, the only way Vallé et al. could serve as an anticipatory reference under 35 U.S.C. §102 is if the disclosed antibody specifically inhibits the binding of human B7.1 antigen to CD28, but does not inhibit the binding of B7.1 antigen to CTLA-4.

Applicants have carefully reviewed the Vallé et al reference, however, it does not appear that this reference teaches or suggests an antibody that meets this functional limitation. In particular, it would appear that the reference is directed to a monoclonal antibody that, by analogy, inhibits both CD28-mediated and CTLA-4-mediated adhesion.

For instance, on page 533, first column, Vallé et al. indicates that to establish binding specificity of the disclosed antibody, competition studies were performed with the anti-B7 antibody disclosed in Freedman et al., 1987. This antibody completely blocked the binding of monoclonal antibody 104 and vice versa.

However, the Freedman antibody also happens to be one of the first antibodies whose specificity was correlated with antibody BB-1 (see Linsley et al., Proc. Natl. Acad. Sci. USA (1990) 87: 5034, col. 2, last full paragraph, submitted in the Information Disclosure Statement dated March 16, 1998). Also, Vallé et al. indicates that the 104 antibody likely binds to the same epitope or one that is very close to that of Freedman et al. Id. Therefore, it is reasonable to assume by analogy that the 104 antibody also would inhibit the B7/CTLA-4 interaction, similar to the BB-1 antibody.

As Applicants respectfully pointed out in the Response to the last Office Action submitted October 14, 1997, monoclonal antibody BB-1 does <u>not</u> meet the limitations of the claimed invention. The fact that monoclonal antibody BB-1 inhibits B7.1/CTLA4 interaction is further supported by the references submitted in the IDS on March 16, 1998. For instance, in Linsley '131, col. 22, l. 9-26, it is reported that mAb BB-1 significantly inhibits the interaction of CTLA4Ig with B7Ig. Because Freedman's anti-B7 was originally identified as having the same specificity as BB-1, and BB-1 <u>inhibits B7.1 and CTLA-4 interaction</u>, by analogy, Freedman's anti-B7 would have the same property. This is also appar-

ent based on the binding experiments disclosed in the present application.

Finally, the Office Action rejects claims 29-32 and 37 under 35 U.S.C. §102(b) as being anticipated by the B7-24 antibody disclosed in Van Gool. However, not only does Van Gool not disclose an antibody that inhibits CD28/B7 interaction but not CTLA-4/B7 interaction, but Van Gool specifically teaches away from isolating such an antibody.

For instance, on page 182, col. 1, the reference states that "it has become crucial to develop and evaluate alternative approaches [for suppressing immune reactions in transplantation], and interfering with B7-CD28/CTLA-4 interaction offers one such possibility." Thus, although this is a rejection under 35 U.S.C. §102, it seems pertinent to point out that the skilled artisan, in reading the disclosure of Van Gool, would not be motivated to isolate antibodies that block B7 interaction with CD28 but not CTLA-4. At no point does Van Gool disclose that the B7-24 antibody inhibits CD28/B7 interaction but not that of B7 and CTLA-4.

Because the cited references make absolutely no mention that the disclosed antibodies fail to inhibit CTLA-4/B7 interaction, the strategy used in the Office Action appears to be one which

requires Applicant to show that every monoclonal antibody disclosed that inhibits CD28/B7 interaction does not also inhibit interaction with CTLA-4 as a matter of inherency.

Where an Examiner has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, the Examiner possesses the authority to require an applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. Nevertheless, before an applicant can be put to this burdensome task, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art... Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. (With emphasis.) Ex Parte Skinner, 2 USPQ2d 1788, 1789 (PTO Bd App & Int 1987).

If inherency *could* be established by probabilities, then the probabilities in this case weigh in Applicants' favor. It has been known in the art for some time that B7 binds to both CD28

and CTLA-4, and that this is due to the sequence and structural homology between the two molecules. Indeed, murine CTLA-4 and CD28 cDNAs demonstrate approximately 76% homology (Harper et al. (1991) J. Immunol.147: 1037; Howard et al. (1991) Immunogenet. 33:74). Because of this homology, CTLA-4 was postulated to play a role in T-cell activation, which is precisely opposite of what its actual role has now been determined to be.

As reported in the draft manuscript attached to Applicants' previous Response dated October 14, 1997, CTLA-4 is now known to play a role in down-regulating immune responses after antigen exposure. In view of this disclosure, it has now become an important goal to isolate antibodies that block CD28/B7 interactions but leave negative regulatory CTLA-4/B7 interactions intact, i.e. for the purpose of more effectively inhibiting T-cell activation in graft rejection and autoimmune disease. But before this realization, it was the goal of the skilled artisan to isolate antibodies that inhibited both CD28 and CTLA-4 interactions with B7, as exemplified by the discussion in Van Gool. Thus, the antibodies of the prior art would be more likely to inhibit both types of interactions, if probabilities were the standard for determining inherency (which they are not), and if

the goals of the skilled artisan were evaluated correctly by the level of knowledge in the art at the time.

But because some valid scientific reasoning must be presented to support an assertion of inherency, and further, because Applicants have clearly presented valid arguments why the antibodies of the prior art do not meet the claimed limitations, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) in view of Razi-Wolf, Vallé or Van Gool is respectfully requested.

Beginning on page 3, the Office action also rejects claims 29-37 under 35 U.S.C. §103 as being unpatentable over any of the above references in view of Linsley '131 or Linsley '288 and art-known procedures for generating recombinant antibodies as disclosed in the specification. Specifically, the Office Action states at the bottom of page 3 that "although these primary references are silent about whether the particular B7 [antibodies] block B7:CTLA-4 interactions per se, all of these references *provide motivation to use the particular specificity* of said B7-specific antibodies as immunosuppressants, [etc.]."

Again, Applicants' respectfully note that neither Razi-Wolf nor Vallé even mention CTLA-4, so they certainly do not provide

motivation for using antibodies which specifically fail to inhibit the interaction of CTLA-4 with one of its natural ligands. Further, Van Gool only mentions the goal of disrupting both CD28/B7 and CTLA-4/B7 interactions, as discussed above, and in fact teaches away from isolating B7 antibodies that fail to inhibit CTLA-4/B7 interaction. Given the belief in the art at the time that CTLA-4, like CD28, was also involved in T cell activation, not down-regulation, it is unclear to Applicants how the cited references provide the motivation for using antibodies that do not inhibit CTLA-4/B7 interaction.

In this regard, Applicants respectfully point out that obviousness is tested by what the combined teachings of the references would have suggested to one of ordinary skill in the art. Before obviousness may be established, the examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles. Ex parte Kranz, 19 USPQ2d 1216, 1218 (PBAI 1991).

The Office Action goes on to state that the two Linsley patents "teach the important role of CD28:B7 interactions in regulating immune responses, [and] inhibiting said immune re-

sponses with B7-specific antibodies... The recombinant techniques ... as taught by the references would have resulted in the same or very nearly the same characteristics of the instant claims since both the references and the instant invention *use the same techniques, the same antibody specificities and the same goals*."

The Examiner is correct in pointing out that Linsley discloses "the important role of CD28:B7 interactions in regulating immune responses, [and] inhibiting said immune responses with B7-specific antibodies." However, instant claim 29 is also limited to B7-specific antibodies which do not inhibit CTLA-4/B7 interactions, because it is now known that, in contrast to CD28/B7 interaction, CTLA-4/B7 interaction down-regulates immune responses.

Applicants have carefully reviewed the Linsley patents, and at no point does Linsley teach or suggest B7-specific antibodies which do not inhibit the interaction of B7 with CTLA-4. In fact, the '131 patent discloses the CTLA4Ig fusion protein and its use to inhibit T and B cell interactions, and specifically the interaction of the B7 receptor with both CD28 and CTLA-4 (col. 11, l. 38-42). The '131 patent also discloses anti-B7 monoclonal antibodies, however, the disclosed antibodies are also used to in-

hibit the interaction of the B7 receptor with both CD28 and CTLA-4 (col. 13, l. 44-47).

Linsley '288, on the other hand, makes absolutely no mention of CTLA-4. This patent discloses CD28Ig and B7Ig fusion proteins, as well as CD28 and B7 antibodies, and their use to inhibit CD28-B7 interactions, but the invention appears to have been made before there was even knowledge in the art that CTLA-4 was a counter receptor. Therefore, there is certainly no motivation in Linsley '288 for the skilled artisan to design B7-specific antibodies which specifically fail to inhibit CTLA-4/B7 interaction. Furthermore, as discussed in Applicants' response filed October 14, 1998, the only B7-specific antibody disclosed in Linsley '288 is the BB-1 antibody, which does not inhibit CTLA-4/B7 interaction. Thus neither Linsley patent makes up for the deficiencies of the primary references in establishing a *prima facie* case of obviousness.

The Office Action goes on to state on page 4 that "the claims do not require that one generate the exact same antibody as the instantly disclosed antibodies, but rather isolates an antibody *that has the same functional characteristics*... The claimed functional limitations *are expected properties of B7-specific*

inhibitory antibodies." Applicants respectfully traverse this line of reasoning.

Again, the antibodies disclosed in the cited references do not have "the same functional characteristics" as those recited in the instant claims. Because the claimed antibodies do not inhibit CTLA-4/B7 interactions, and those of the prior art do inhibit CTLA-4/B7 interactions as established above, the antibodies of the prior art and those recited in the claims are not functionally identical. Again, because it has now been established that CTLA-4-B7 interaction acts to down-regulate immune responses, antibodies that fail to inhibit this interaction would be expected to be more efficient at inhibiting immune responses since the natural regulatory interaction of CTLA-4/B7 is not disturbed.

Furthermore, as discussed above, the claimed functional limitation of failing to inhibit CTLA-4/B7 interaction is not "an expected property" of a B7-specific antibody. Because B7 binds to both CTLA-4 and CD28, and CTLA-4 and CD28 have a high degree of homology, antibodies that bind to B7 and inhibit its interaction with CD28 would be expected to also inhibit interaction with CTLA-4.

As described in the draft manuscript attached to Applicants' Response dated October 14, 1997, Applicants isolated the claimed antibodies following immunization of cynomolgus primates, and engineered the isolated antibodies into PRIMATIZED® versions by substituting human constant regions. It was both fortunate and unexpected in view of the now understood role of CTLA-4 that Applicants were able to isolate antibodies to human B7.1 that fail to inhibit CTLA-4 interaction using the disclosed method.

Indeed, as described on page 16 of the draft manuscript, antibody P16C10 recognizes a specific site on B7.1 that is distinct from epitopes recognized by CTLA-4 or antibodies such as L307.4 or BB-1 which inhibit the binding of CTLA-4. The fact that Applicants were successful in isolating an antibody with the claimed characteristics that does not recognize rhesus B7.1 is intriguing because recent sequence information suggests that there are only six variations from complete homology in the extracellular domain between human and rhesus B7.1 (draft manuscript, p. 16).

Thus, antibody P16C10 and others with the same properties isolated by the disclosed method likely recognize a functional yet undefined site in human B7.1 which is absent in lower pri-

mates. Not only is this epitope absent in lower primates, but it just happens to be involved in human CTLA-4/B7 interaction. The chances of such an epitope being identified when there are only six variations between the sequence of the human and rhesus B7.1 molecules is an unexpected, advantageous property of Applicants' particular screening method.

The Office Action appears to suggest, as discussed above, that the cited references would result in antibodies having the same properties because the references and the instant invention *use the same techniques, the same antibody specificities and the same goals*. Applicants respectfully disagree.

The goals of the published studies were certainly not to isolate B7 antibodies that do not inhibit CTLA-4/B7 interaction, as discussed at length above. Furthermore, although the techniques employed in the prior art may have been mechanistically similar, the cited references do not isolate human B7-specific antibodies by immunization of cynomolgus monkeys.

Razi-Wolf et al. describe the isolation of a <u>hamster anti-murine B7</u> antibody; the monoclonal antibodies described in Vallé and Van Gool were isolated by immunizing <u>mice</u> with human cells. Thus, although antibodies which recognize epitopes <u>not involved</u>

in CTLA-4 interaction may have possibly been isolated by the methods described in the prior art, the authors would have had to screen for antibodies having such a specificity. Only Applicants' screening method has been demonstrated to readily yield antibodies which recognize a human B7.1 epitope which is not involved in CTLA-4 interaction, by virtue of one of the six differences in homology between human and rhesus B7.1.

Because human and primates have likely diverged on an evolutionary scale to a much lesser degree than human versus mouse, the variety of antibodies obtained by immunizing mice with human B7.1-expressing cells is likely to encompass many more epitope specificities than would be achieved by immunizing a primate which expresses B7.1 having only six sequence variations from that found in humans. As a result, many more antibodies would have to be screened from the immunized mouse before a B7.1-specific antibody was found that inhibits CD28 interaction but not CTLA-4, because a much greater variety of antibodies would be expected due to the evolutionary differences between the human and murine B7.1 molecules.

Thus, it cannot be said that the cited references *use the same techniques* because the immunization protocol of the present

invention presents distinct advantages over the immunization protocols of the prior art. Again, this is because a larger majority of the primate human B7.1-specific antibodies isolated will meet the limitation of the instant claims due to the one or more unexpected epitopes which are (i) not present in lower primates, (ii) result in antibodies that inhibit CD28/B7 interaction, and (iii) fail to inhibit the interaction of human CTLA-4 and B7.1.

Indeed, the present case may be distinguished from that of Ex parte Goodall, where the PTO Board of Appeals and Interferences found that where an appellant claimed a new monoclonal antibody and where the prior art produced antibodies using the same antigen, mouseline and myeloma cell line as the appellant, the processes are sufficiently similar so that the antibodies produced by the hybridomas could reasonably be expected to be the same. Ex Parte Goodal, 231 USPQ 831, 832 (1985).

Here, the prior art processes do not use the same immunized animal or myeloma cells, so a different array of antibodies would be expected. Furthermore, the fact that antibodies have been generated which recognize a distinct, formerly undescribed site on human B7.1 is truly unusual and unexpected given the fact that

B7.1 has been so highly conserved between human and primates. The Federal Circuit has clearly established that one way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward- that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results. In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

Thus, Applicants respectfully submit that the claimed antibodies are neither disclosed nor suggested by any of the primary references. Moreover, the secondary references, i.e., the Linsley patents, clearly do not make up for the deficiencies of the primary references. Not only are the claimed antibodies functionally distinguishable from those of the prior art, but one of ordinary skill in the art would not have the same likelihood of identifying an antibody having the same functional character-

istics unless a similar immunization protocol in a similar species was adopted. And even if particular epitopes defining the claimed antibodies were known, absent some motivation in the cited art for isolating an antibody that inhibits CD28/B7 interactions but not that of CTLA-4/B7, a *prima facie* showing of obviousness has not been established. For all these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 29-37 under 35 U.S.C. §103.

The foregoing Remarks constitute a full Response to the Office Action. Accordingly, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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